



Provocholine[®]
[methacholine chloride powder for inhalation]

Taking the Provocholine Challenge Training Program

(Self Study Module)

Version 5.0

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Introduction

Course Objectives

At the completion of this course, the learner should be able to describe the:

- pharmacology of methacholine
- personnel requirements and training
- indications and contraindications for a methacholine challenge test (MCT)
- preparation of equipment and supplies for the MCT
- method for checking output of nebulizers
- patient preparation steps and assessment
- laboratory quality assurance

1

Introduction

Course Objectives

At the completion of this course, the learner should be able to list and discuss:

- indications, contraindications, and safety factors for a methacholine challenge test
- steps for performing an MCT by tidal breathing or dosimeter technique
- methods to report the results of an MCT
- interpretation of the MCT
- additional factors that may influence the results

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Introduction

Course Accreditation

- This self-study course has been approved for 2.0 CRCE hours through the AARC as a non-traditional course
- After reviewing the course material, the applicant must complete an on-line post-study evaluation at www.provocholine.com/ssm/
- AARC members will be required to provide their AARC number along with some basic information to obtain credits
- A post-survey questionnaire will be available to applicants upon completing the post-study evaluation
- A passing grade of 75% is required to receive a certificate of completion and AARC membership numbers will be registered within 30 days
- We gratefully acknowledge Susan Blonshine RRT, RPFT, FAARC, AE-C, TECHED CONSULTANTS INC for her invaluable assistance in the preparation of “Taking the Provocholine® Challenge” testing materials.

1

Introduction

Provocholine® (methacholine chloride):

- Originally received FDA approval in 1986
- Licensed to Methapharm in 1996
- Is indicated for the diagnosis of bronchial airway hyperreactivity in subjects who do not have clinically apparent asthma, especially in patients with unclear or nonspecific symptoms

1 Introduction

Definition of Asthma Control

Asthma Control is defined as the extent to which the various manifestations of asthma have been reduced or removed by treatment – it includes two components:

- the level of clinical asthma control including lung function
- the risk of future adverse events including an accelerated decline in lung function

Reddel H, Taylor RD, Bateman ED, *et al.* An official American Thoracic Society/European Respiratory Society statement: Asthma control and exacerbations – Standardizing endpoints for clinical asthma trials and clinical practice. *American Journal of Respiratory and Critical Care Medicine* 2009; 180: 59-99

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Pharmacology

Provocholine[®] (methacholine chloride) is:

- A parasympathomimetic (cholinergic) bronchoconstrictor to be administered in solution only, by inhalation, for diagnostic purposes
- The β -methyl homolog of the neurotransmitter acetylcholine, a substance that occurs naturally in the body, but has a longer duration and is more selective
- Metabolized more slowly than acetylcholine by cholinesterase

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Pharmacology

Pharmacologic basis of Provocholine[®]:

- Bronchial smooth muscle contains significant parasympathetic (cholinergic) innervation
- Bronchoconstriction occurs when the vagus nerve is stimulated and acetylcholine is released from the nerve endings - subjects with asthma are markedly more sensitive to methacholine-induced bronchoconstriction than are healthy subjects
- This difference in response is the pharmacologic basis for the Provocholine[®] inhalation diagnostic challenge

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Pharmacology

Provocholine[®] is a direct challenge test:

Direct Challenge Tests:

- Act directly on airway receptors
- Have a high negative predictive value, and therefore very few false-negative tests
- Examples include Provocholine (methacholine chloride) and histamine
- High specificity

Indirect Challenge Tests:

- Act through intermediate pathways as mast cell mediators are released by adenosine monophosphate
- Have a higher positive predictive value
- Examples include hypertonic aerosols, exercise, cold air, hyperventilation

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Indications

The primary indication for a methacholine challenge test is to rule out a diagnosis of current asthma in those individuals who have symptoms which may suggest asthma.

Provocholine[®] (methacholine chloride powder for inhalation) is indicated for the diagnosis of bronchial airway hyperreactivity in subjects who do not have clinically apparent asthma.

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Indications

According to the American Thoracic Society Guidelines for Methacholine and Exercise Challenge Testing – 1999:

- Methacholine challenge testing is most often considered when asthma is a serious possibility and traditional methods, most notably spirometry performed before and after administration of a bronchodilator, have not established or eliminated the diagnosis. (i.e. post-bronchodilator response was not significant in that the increase in FEV₁ or FVC \leq 12% and \leq 200 mL)
- Methacholine challenge testing is also a valuable tool in the evaluation of occupational asthma.

3

Indications

When to consider using a Methacholine Challenge Test

According to the NAEPP Guidelines for the Diagnosis and Management of Asthma:

- Research indicates that airway hyperresponsiveness is important in the pathogenesis of asthma and that the level of airway responsiveness usually correlates with the clinical severity of asthma
- While the relationship between airway inflammation and airway responsiveness is complex:
 - Airway markers of inflammation correlate with bronchial hyperresponsiveness
 - Treatment of asthma and modification of airway inflammatory markers not only reduces symptoms but also diminish airway responsiveness

3

Indications

When to consider using a Methacholine Challenge Test

According to the ACCP Clinical Practice Guidelines:

Diagnosis and Management of Cough:

- For patients who present with an unexplained chronic cough (lasting longer than 8 weeks) and where empiric treatment for upper airway cough syndrome (UACS) does not resolve or only partially resolves the cough
- If spirometry does not indicate reversible airflow obstruction [bronchoprovocation challenge] should be performed in the evaluation of asthma as a cause of cough

3

Indications

When to consider using a Methacholine Challenge Test

In addition to using the MCT to exclude a diagnosis of airway hyperreactivity (i.e. asthma), uses of the MCT may include:

- The need to establish a diagnosis of asthma
- The need to evaluate occupational asthma
- The need to assess (and document) the severity of asthma

American Thoracic Society Guidelines for Methacholine and Exercise Challenge Testing – 1999 (Published in American Journal of Respiratory & Critical Care Medicine, Vol. 161:1, January 2000, pp. 309 – 329)

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Indications

When to consider using a Methacholine Challenge Test

Additional uses of the MCT may include:

- The need to determine the relative risk of developing asthma
- The need to determine who is at risk in the military or workplace
- The need to assess response to therapeutic interventions

American Thoracic Society Guidelines for Methacholine and Exercise Challenge Testing – 1999 (Published in American Journal of Respiratory & Critical Care Medicine, Vol. 161:1, January 2000, pp. 309 – 329)

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Contraindications

Contraindications – Absolute

MCT is absolutely contraindicated for patients with:

- Known hypersensitivity to methacholine chloride or other parasympathomimetic agents
- Severe airflow limitation ($FEV_1 < 50\%$ predicted or $FEV_1 < 1.0$ L)
- Heart attack (myocardial infarction) or stroke (CVA) within the previous 3 months
- Uncontrolled hypertension (systolic BP > 200 and/or diastolic BP > 100 mm Hg)
- Known arterial aneurysm

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Contraindications

Contraindications – Relative*

The following are relative contraindications of the MCT:

- Airflow limitation (reduced FEV₁/FVC ratio) and FEV₁ < 60% predicted or < 1.5 L
- Inability to perform acceptable/repeatable spirometry at baseline
- Pregnant or nursing mothers
- Current use of cholinesterase inhibitor medication

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Contraindications

Contraindications – Relative* (continued)

The following are relative contraindications of the MCT:

- Significant response to diluent (i.e. FEV₁ falls > 10% from baseline after administration of saline solution not containing any methacholine chloride)
- Upper or lower respiratory-tract infection within previous 2-6 weeks
- Patients receiving any beta-adrenergic blocking agent

* MCT should only be performed if a physician determines that the benefits clearly outweigh the risks

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Understanding the MCT

Factors That May Affect MCT Results

- Spirometry may not be sensitive or specific enough in some patients to detect changes
- The deep inspiration required for spirometry may alter bronchial tone
- Failure to withhold medications that may affect the bronchial reactivity test or failure to hold for a sufficient time prior to the challenge

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Understanding the MCT

Factors That May Affect MCT Results (continued)

- Variable results may occur based on the time of day testing is performed
- Ingestion of foods containing caffeine may decrease bronchial responsiveness
- Improper preparation or storage of methacholine solutions
- Inconsistencies in technique and equipment used for the test

5

Understanding the MCT

Factors That May Affect MCT Results (continued)

- Patient's inability to perform acceptable spirometric maneuvers
- Test is effort and technique dependent
- Smoking
- Occupational sensitizers
- Specific antigens
- Upper or lower respiratory-tract infection

5

Understanding the MCT

Possible Complications of the MCT

- Bronchoconstriction
- Hyperinflation
- Severe coughing
- Spirometry related dizziness, light headedness, chest pain
- Systemic hypotension

5

Understanding the MCT

Personnel Qualifications

While no recognized certification program exists for persons performing the MCT, the ATS recommends that at a minimum, a technologist performing challenge tests should:

- be familiar with current guidelines & test procedures
- be capable of managing and maintaining equipment
- be proficient at spirometry and/or plethysmography
- know the contraindications of the MCT

5

Understanding the MCT

Personnel Qualifications (continued)

- be familiar with safety and emergency procedures
- be familiar with guidelines for bronchodilator administration
- know when to stop further testing
- have performed at least 20 MCT procedures under direct supervision

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Equipment and Supplies

- Methacholine (Provocholine®)
- Diluent
- Dosimeter
- Nebulizer
- Compressed gas source, flow meter, and tubing
- Calibrated spirometer
- Timer
- Bronchodilator
- Oxygen delivery system
- Stethoscope
- Sphygmomanometer
- Pulse oximeter

6

Equipment and Supplies

Preparation of Provocholine[®] Solutions

- Must be performed by a pharmacist or other properly trained individual using sterile technique
- A sterile bacterial-retentive filter (porosity 0.22 μm) should be used when transferring solutions to a nebulizer
- Measures should be taken to minimize technologist exposure to methacholine aerosol
- Accurate sterile mixing is very important for the accuracy of the test results and for the safety of patients

6

Equipment and Supplies

Preparation of Provocholine®

Clearly label each vial of solution*

Concentration (Strength)

Diluent used*

Preparation Date*

Expiration date

Lot number (from Provocholine® vial)

Initials of individual preparing solution*

Strength:		Provocholine® Mfr. Lot No. P- Initials	www.methapharm.com
Diluent:			
Prep. Date:	/ /		
Exp. Date:	/ /		

* Fill in all sections of green labels provided with Provocholine®

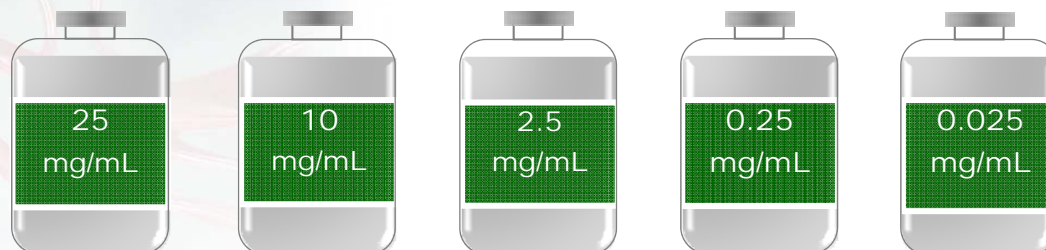
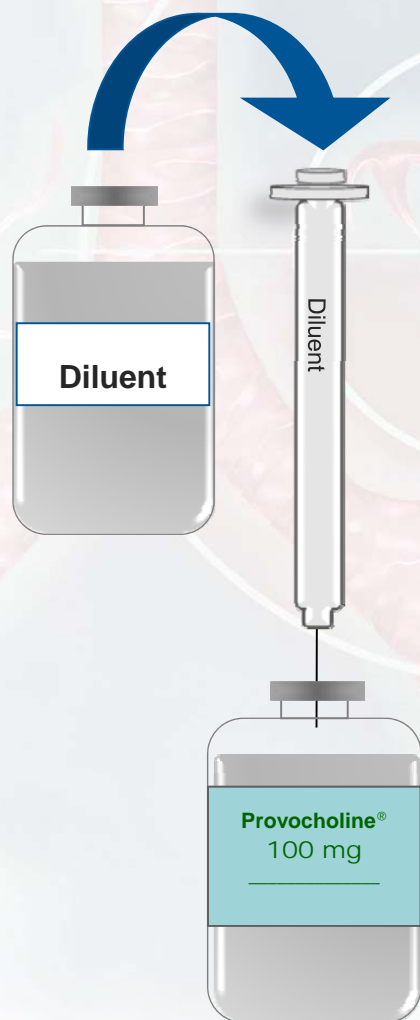
6

Equipment and Supplies

Preparation of Provocholine® Solutions

Following the Provocholine® package insert for all instructions and safety information, the serial concentrations are prepared as follows:

1. Add 4 mL of diluent to the vial containing 100 mg of Provocholine® resulting in 4 mL of the 25 mg/mL solution (shake well)
2. Draw 1 mL of the 25 mg/mL solution and add 1.5 mL of Diluent resulting in 2.5 mL of the 10 mg/mL solution (shake well)
3. Draw a further 1 mL of the 25 mg/mL solution and add 9 mL of Diluent resulting in 10 mL of the 2.5 mg/mL solution (shake well)
4. Draw 1 mL of the 2.5 mg/mL solution and add 9 mL of Diluent resulting in 10 mL of the 0.25 mg/mL solution (shake well)
5. Draw 1 mL of the 0.25 mg/mL solution and add 9 mL of Diluent resulting in 10 mL of the 0.025 mg/mL solution (shake well)



6

Equipment and Supplies

Preparation of Provocholine®

- Refrigerate reconstituted solutions at 36° to 46°F (2° to 8°C) for up to 2 weeks – lowest dilution should be prepared the day of the test
- Freezing does not affect stability of dilutions A through D – Vial E must be prepared on the day of the challenge
- Consult package insert for dilution sequence
- Additional stability information available in published resources

6

Equipment and Supplies

Nebulizers

Two-minute Tidal Breathing Technique

- Nebulizer must deliver aerosol with particle mass median diameter (MMD) between 1.0 and 3.6 μm
- Avoid nebulizers with particle MMD $< 1.0 \mu\text{m}$
- Flow meter should be adjusted to deliver an output within 10% of 0.13 mL/minute
- Nebulizers should be properly calibrated in order to determine the flow meter setting (at pressure = 50 PSI)

6

Equipment and Supplies

Nebulizers

Dosimeter Method

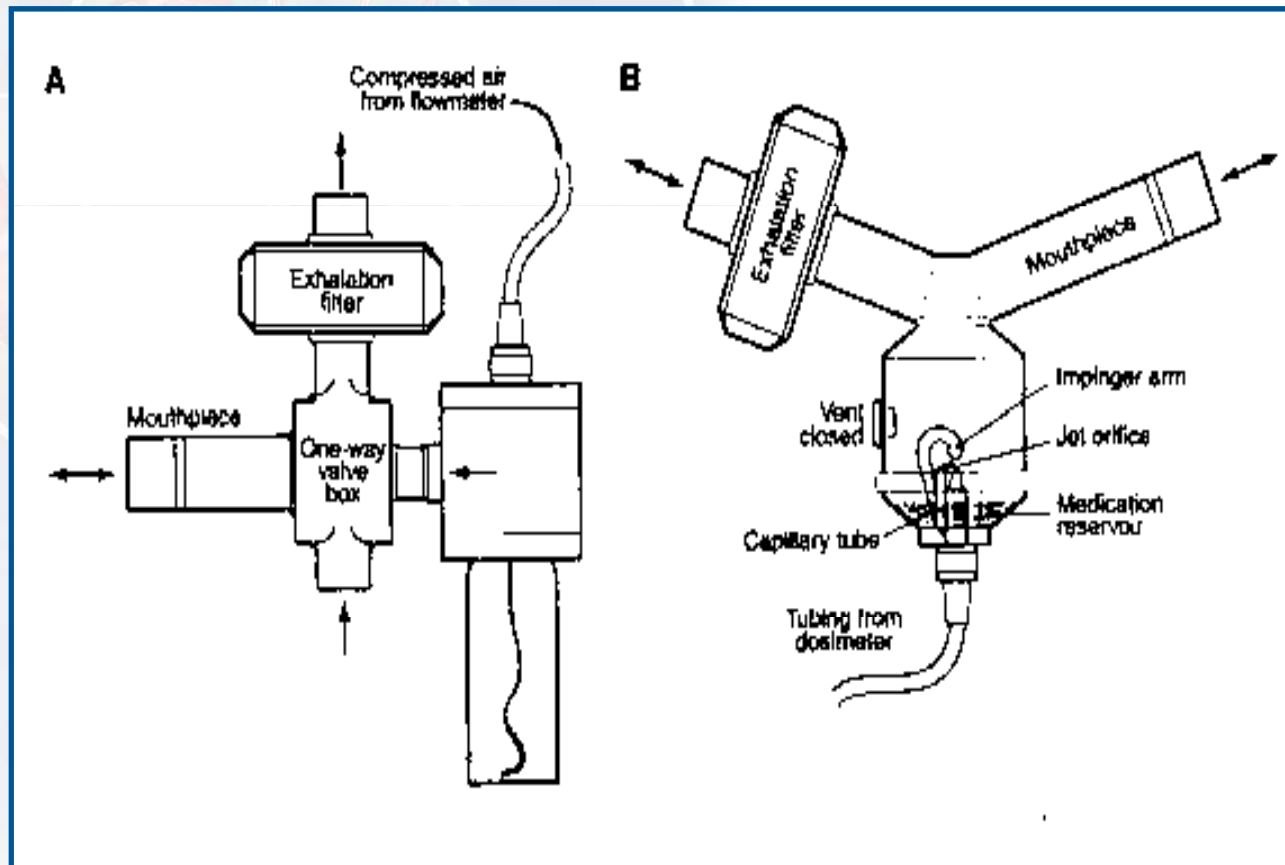
Dosimeters are aerosol generating devices designed for precise administration of broncho-provocation agents.

- Select a high quality nebulizer with an aerosol particle size $\leq 3 \mu\text{m}$
- Nebulizer should deliver $9 \mu\text{L}$ (0.009 mL) $\pm 10\%$ of solution per 0.6 second actuation during inhalation for the five breath dosimeter technique (Example B on next slide: Devilbiss 646)
- Consult dosimeter manufacturer for specific nebulizer recommendations
- A $\pm 10\%$ range in nebulizer output is considered acceptable with doubling or quadrupling concentration increments
- Use the same nebulizer throughout the challenge due to internebulizer variability

6

Equipment and Supplies

Nebulizers (examples A and B from previous slide)



6

Equipment and Supplies

Nebulizers

- Flow meter accuracy should be checked with a rotameter
- Nebulizer output should be checked since output varies from model to model, unit to unit and may vary over time
- ATS recommends checking nebulizer output initially and every 20 uses (output can be checked by measuring the change in weight of a nebulizer filled with saline solution before and after 10 activations)

6

Equipment and Supplies

Calibration and Maintenance



- Check nebulizer output
- Number all nebulizers
- Measure output before first using it and after every 20 uses as suggested by the ATS

7 Equipment Quality Control

Measuring Output without Dosimeter

Dosimeters are aerosol generating devices designed for precise administration of broncho-provocation agents.

- Place approximately 2 mL of saline or distilled water in nebulizer
- Weigh nebulizer using a scale that measures accurately to 0.001 g
- Apply a known level of airflow to the filled nebulizer, using a calibrated pressure-compensated flow meter

7 Equipment Quality Control

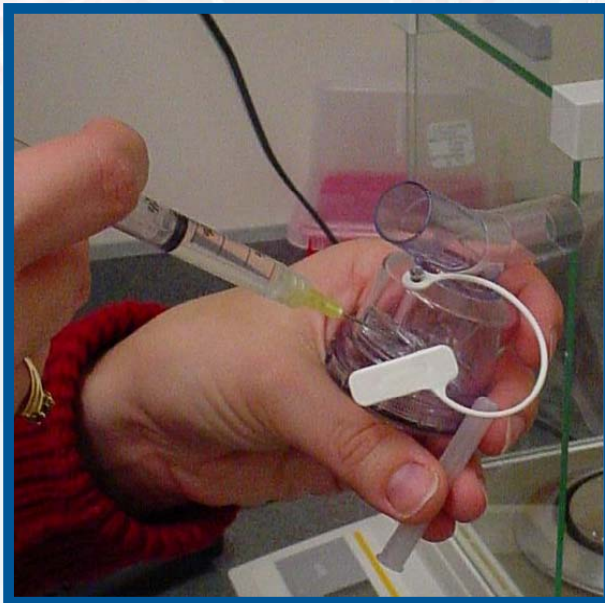
Measuring Output without Dosimeter

- Continue the nebulization for a specific period of time (e.g., 2 minutes)
- Reweigh the nebulizer and divide the change in weight by the number of minutes
- Repeat this process at different flow rates (e.g., 7, 8, 9, 10 L/min) and create a graph of nebulizer output (i.e., weight loss) in mL/min versus airflow (assume 1 mL of water or saline equals 1 g)

7 Equipment Quality Control

Measuring Output with a Dosimeter

- Place approximately 2 mL of saline or distilled water in nebulizer (vent, if applicable, should be closed)



7 Equipment Quality Control

Measuring Output with a Dosimeter

- Weigh the nebulizer using a scale that measures accurately to at least 0.5 milligrams



7 Equipment Quality Control

Measuring Output with a Dosimeter

- Connect nebulizer to dosimeter (dosimeter nebulization time set at 0.6 s and dosimeter powered by 20 psi of compressed air)



7 Equipment Quality Control

Measuring Output with a Dosimeter

- Actuate the dosimeter manually ten times. Optionally, a 3.0 L calibrating syringe can be used to exert an inspiratory capacity and trigger the dosimeter
- Reweigh the nebulizer and divide the change in weight by the number of times the dosimeter was actuated to obtain the nebulizer output in mL/breath



7 Equipment Quality Control

Measuring Output with a Dosimeter

- Nebulizer output may be variable depending on many factors, but is typically between 0.005 and 0.03 mL/actuation
- Nebulizer output measured multiple times on the same nebulizer should be reproducible to within 10%.

8

Preparing for the MCT

Pre-test Preparation Patient Instructions

Withholding Medications Prior to Test

Inhaled Bronchodilators:

- Short-acting (e.g. *albuterol*) 8 hrs
- Long-acting (e.g. *salmeterol, tiotropium**) 48 hrs

Oral Bronchodilators:

- Liquid theophylline 12 hrs
- Intermediate-acting theophylline 24 hrs
- Long-acting theophyllines 48 hrs
- Standard β_2 -agonist tablets 12 hrs
- Long-acting β_2 -agonist tablets 24 hrs

* Perhaps up to 1 week for tiotropium

* THE EFFECTS OF NEWER MEDICATIONS HAVE NOT BEEN INVESTIGATED

8

Preparing for the MCT

Pre-test Preparation Patient Instructions

Withholding Medications Prior to Test (continued)

- Cromolyn Sodium 8 hrs
- Leukotriene Modifiers 24 hrs
- Nedocromil 48 hrs
- Hydroxazine, Cetirazine 3 days
- Anticholinergics 24 hrs
- Leukotriene modifiers 24 hrs

** THE EFFECTS OF NEWER MEDICATIONS HAVE NOT BEEN INVESTIGATED*

8

Preparing for the MCT

Dosing Schemes

Provocholine® Package Insert Dosing Concentrations

0	(Diluent)
0.025	mg/mL
0.25	mg/mL
2.5	mg/mL
10.0	mg/mL
25.0	mg/mL

At each concentration, five breaths are administered by a nebulizer that should deliver 9 μ L (0.009 mL) \pm 10% of solution per 0.6 second actuation during inhalation by a breath-activated timing device (dosimeter)

8

Preparing for the MCT

ATS Dosing Schemes

10 Doubling concentrations

0	(Diluent)
0.03	mg/mL
0.06	mg/mL
0.125	mg/mL
0.25	mg/mL
0.5	mg/mL
1.0	mg/mL
2.0	mg/mL
4.0	mg/mL
8.0	mg/mL
16.0	mg/mL

8

Preparing for the MCT

ATS Dosing Schemes

Fourfold dose increase with Dosimeter Method

0	(Diluent)
0.0625	mg/mL
0.25	mg/mL
1.0	mg/mL
4.0	mg/mL
16.0	mg/mL

8

Preparing for the MCT

Dosing Schemes

Starting Concentrations for Children (CTS Guidelines)

If $FEV_1/VC > 80\%$ AND the child's symptoms are well controlled on the following medications, use these starting concentrations:

- No medications 0.25 mg/mL
- Daily or occasional bronchodilators 0.06 mg/mL
- Inhaled or ingested corticosteroids 0.03 mg/mL

If $FEV_1/VC < 80\%$ OR if asthma symptoms do not appear to be well controlled
DO NOT OMIT ANY CONCENTRATIONS – start all patients at 0.03 mg/mL

NOTE: Canadian Thoracic Society (CTS) Guidelines refer to the ATS Two-minute tidal breathing method.

8

Preparing for the MCT

Special Considerations For Pediatrics

- Provocholine® is FDA approved for patients 5 years of age and older and may be performed in children who can perform good quality spirometry or body plethysmography
- Children may need to perform more trials to achieve repeatability
- Technologists must be trained in age appropriate instructions and encouragement techniques to achieve valid test results in children

9

Pre-test Preparation

Patient Instructions

Other Considerations

- The ATS does not recommend routinely withholding oral or inhaled corticosteroids, but their anti-inflammatory effect may decrease bronchial responsiveness
- Antihistamines are generally not withheld
- Withholding beta-adrenergic blocking agents or performing MCT with these agents should be done with caution and ONLY on specific orders of the ordering physician
- Coffee, tea, cola drinks and chocolate should be avoided on the day of study

9

Pre-test Preparation

Patient Instructions

- A consent form describing the procedure should be reviewed and signed by the patient or parent/legal guardian.
- Consent forms should not provide information that would lead the patient to a suggestion of a specific outcome.
- The procedure should be thoroughly explained to the patient prior to the procedure. This includes how to inhale the solution and perform the required pulmonary function tests.
- It is often helpful to speak to the patient prior to the appointment to review medications and holding times.

9

Pre-test Preparation

Patient Assessment (Pre-test)

- Confirm patient identification, physician order, clinical history and indication for testing
- Assess each patient's ability to perform the MCT
- Ensure the patient has complied with the preparation criteria including recent illnesses and withholding medications as required

9

Pre-test Preparation

Equipment Preparation

- Remove the methacholine from the refrigerator 30 minutes prior to testing to allow it to warm to room temperature
- The temperature impacts nebulizer output
- Check all equipment to ensure it is working properly
- Calibrate the PF systems each day of use prior to the challenge testing
- Ensure bronchodilators, oxygen, and emergency equipment is available

10 Performing the MCT

Both Methods

- Check for complete physician's order, history and medications list
- Collect and record demographic information
- Verify compliance of physician instructions for withholding medications etc.
- Explain procedure and demonstrate the test procedures (tidal breathing or dosimeter method)

10 Performing the MCT

Both Methods

- Perform baseline spirometry according to the most recent ATS criteria.
- Ensure the absence of absolute and relative contraindications
- If the FEV₁ is less than 1.0 L, contact the ordering physician as proceeding is NOT recommended
- Calculate a target FEV₁ that indicates a 20% fall in FEV₁ from baseline (or diluent)*

* 20% fall in FEV₁ is calculated from baseline (initial) only if no diluent step is used. If Diluent step is used, then the target 20% fall in FEV₁ is calculated from the diluent step (i.e. spirometry after administration of saline solution not containing any methacholine chloride)¹

10 Performing the MCT

Select the Delivery Method

- The tidal breathing method requires that at each concentration, patient breathes quietly (tidal breathing) for 2 minutes while solution is administered by a nebulizer with the flow meter set to deliver an output of 0.13 mL/min \pm 10%
- The five-breath dosimeter method requires that at each concentration, five breaths are administered by a nebulizer that should deliver 9 μ L (0.009 mL) \pm 10% of solution per 0.6 second actuation during inhalation by a breath-activated timing device (dosimeter)

10 Performing the MCT

Select the Delivery Method

- If both methods are performed according to the ATS standards, the PC20 will decrease to a larger extent with the tidal breathing method
- A larger dose is delivered with tidal breathing method
- Dosimeter method produces bronchodilation and bronchorestriction in individuals with mild airway hyperresponsiveness (AHR) to methacholine due to the maximal inspirations and breathholds
- Methods are comparable in moderate or greater AHR

10 Performing the MCT

Both Methods

- Using a sterile syringe, insert about 2 mL of diluent into a nebulizer appropriate for the method of testing you have chosen (the amount of solution used must meet nebulizer's fill volume)
- Attach exhalation filter and nose clip
- Begin nebulization with the diluent in the same manner as the methacholine

* 20% fall in FEV₁ is calculated from baseline (initial) only if no diluent step is used. If Diluent step is used, then the target 20% fall in FEV₁ is calculated from the diluent step (i.e. spirometry after administration of saline solution not containing any methacholine chloride)¹

10 Performing the MCT

Dosimeter Method

- Connect the tubing to the nebulizer and dosimeter
- Actuate the dosimeter 2 times to prime the nebulizer and observe adequate nebulization
- Instruct the patient to inhale slowly from FRC to TLC and hold the breath at TLC for 2 to 5 seconds
- Repeat the maneuver until five breaths have been completed.
- Start the timer after the fifth breath has been completed

* 20% fall in FEV_1 is calculated from baseline (initial) only if no diluent step is used. If Diluent step is used, then the target 20% fall in FEV_1 is calculated from the diluent step (i.e. spirometry after administration of saline solution not containing any methacholine chloride)¹

10 Performing the MCT

Dosimeter Method

- Repeat spirometry at 30 sec and 90 sec after the fifth breath
- FEV₁ repeatability should be within 150 mL
- Maneuvers should take no more than three minutes to complete
- Time between two subsequent concentrations should not exceed five minutes

10 Performing the MCT

Dosimeter Method

- If the highest post-diluent FEV₁ is:
 - > 90% of the highest baseline, empty and clean nebulizer thoroughly, and begin to administer the first dose of methacholine
 - < 90% and > 80% of the highest baseline, repeat the diluent step
 - ≤ 80% of the highest baseline, contact the ordering physician

10 Performing the MCT

Dosimeter Method

- Repeat the process until either FEV₁ drops at least 20% from the post-diluent baseline or highest concentration has been administered
- Always prime the dosimeter 2 times
- Ensure repeatability of the FEV₁ (150 mL), but no more than 5 maneuvers
- It may be possible to use an abbreviated FVC time (< 6 seconds), but a full FVC should be completed at baseline and the final dose of methacholine
- Report the highest FEV₁ (2 trials \leq 80% of the highest post-diluent FEV₁ marks completion of the test)
- When the FEV₁ is \leq 80% of the highest post-diluent FEV₁, administer a bronchodilator, wait 10 min and repeat spirometry, ensuring FEV₁ \geq 90% of baseline prior to sending patient home
- A second bronchodilator may be administered if the FEV₁ \geq 90%

10 Performing the MCT

Tidal Breathing

- Power the nebulizer with dry compressed air
- Set the flow meter to 50lb/in²
- Verify flow meter accuracy and set to achieve output previously established during calibration and quality control of the nebulizers
- The patient should be instructed to relax and breathe quietly for 2 minutes with a nose-clip in place

10 Performing the MCT

Tidal Breathing

- Repeat spirometry at 30 sec and 90 sec after the nebulization is complete
- FEV₁ repeatability should be within 150 mL
- Maneuvers should take no more than three minutes to complete
- Time between two subsequent concentrations should not exceed five minutes

10 Performing the MCT

Tidal Breathing

- If the highest post-diluent FEV₁ is:
 - > 90% of the highest baseline, empty and clean nebulizer thoroughly, and begin to administer the first dose of methacholine
 - < 90% and > 80% of the highest baseline, repeat the diluent step
 - ≤ 80% of the highest baseline, contact the ordering physician

10 Performing the MCT

Tidal Breathing

- Repeat the process until either FEV₁ drops at least 20% from the post-diluent baseline or highest concentration has been administered
- Ensure repeatability of the FEV₁ (150 mL), but no more than 5 maneuvers
- It may possible to use an abbreviated FVC time (< 6 seconds), but a full FVC should be completed at baseline and the final dose of methacholine
- Report the highest FEV₁ (2 trials \leq 80% of the highest post-diluent FEV₁ marks completion of the test)
- When the FEV₁ is \leq 80% of the highest post-diluent FEV₁, administer a bronchodilator, wait 10 min and repeat spirometry, ensuring FEV₁ \geq 90% of baseline prior to sending patient home
- A second bronchodilator may be administered if the FEV₁ \geq 90%

10 Performing the MCT

Both Methods

Factors to hold constant to maintain standardization

- Nebulizer output
- Particle size
- Volume inhaled
- Length of breath-hold
- Inspiratory flow rate

11 Test Quality Review

Spirometry Quality

Within-maneuver evaluation

End of test criteria is met if:

- Plateau in the volume-time curve (<25 mL for ≥ 1 second)
OR
- Minimum exhalation time of 6 seconds (3 seconds in children <10 years)
OR
- Patient cannot or should not continue to exhale

Note: Early termination of a maneuver is not a reason to eliminate all the results from that maneuver since information such as FEV_1 may be useful⁶

11 Test Quality Review

Spirometry Quality

Within-maneuver evaluation

Was the start of test criteria met?

- Extrapolated Volume (EV) must be $< 5\%$ of FVC or 150 mL, whichever is greater, to achieve accurate time zero and assure FEV_1 comes from maximal effort curve
- No hesitation or false start to maneuver
- Peak expiratory flow should be achieved with a sharp rise and occur close to start of exhalation (rapid start to rise time)
- No coughing, particularly during the first second of the maneuver

11 Test Quality Review

Spirometry Quality

Between-maneuver evaluation

- After at least 3 acceptable FVC maneuvers have been obtained, apply the following tests:
- Variance less than or equal to 150 mL between largest and second largest FVC
- Variance less than or equal to 150 mL between largest and second largest FEV₁
- If both the above criteria have been met, conclude the evaluation test

11 Test Quality Review

Spirometry Quality

Result Selection and Reporting

- Record largest FVC from acceptable maneuvers
- Record largest FEV₁ from acceptable maneuvers

12 Reporting Results

Reporting

- Always include spirograms with the results
- Technologist should always include their observations:
 - Did the test meet ATS criteria? Why not?
 - Any evidence of medication, technique or history that could distort test?
 - Were symptoms present? If yes, were the symptoms similar to the initial complaint?

12 Reporting Results

Reporting

- Express data as percent of baseline or the post-diluent result
- Present data for each step of the test including the bronchodilator
- For spirometry, report FVC, FEV₁, and the FEV₁/FVC ratio
- For plethysmography, report sGaw or sRaw
- Express each dose in mg/mL

12 Reporting Results

Reporting

- Include percent change and absolute values in both the graphic and tabular display
- Report the concentration which resulted in a 20% decrease in FEV₁.
- Report the concentration which resulted in a 40% decrease in sGaw or a 40% increase in sRaw
- Include technologist comments concerning cooperation, effort, cough response, wheezing, shortness of breath or other symptoms

12 Reporting Results

Reporting

Calculation of PC₂₀

$$PC_{20} = \text{antilog} \left[\log C_1 + \frac{(\log C_2 - \log C_1) (20 - R_1)}{R_2 - R_1} \right]$$

Where:

C₁ = methacholine concentration preceding C₂

C₂ = methacholine concentration causing a ≥ 20% drop in FEV₁ from baseline

R₁ = percent fall in FEV₁ after C₁

R₂ = percent fall in FEV₁ after C₂

13 Interpretation of the Results

Interpretation of Results

Categorization of Bronchial Responsiveness (ATS)

PC ₂₀ Results	Interpretation*
>16 mg/mL	Normal bronchial responsiveness
4-16 mg/mL	Borderline bronchial hyper-responsiveness (BHR)
1-4 mg/mL	Mild BHR
<1 mg/mL	Moderate – Severe BHR

* This method of interpretation assumes:

- baseline airway obstruction is absent
- spirometry quality is good
- there is substantial post-challenge FEV₁ recovery

13 Interpretation of the Results

Interpretation of Results

- The positive predictive value increases the closer the PC₂₀ is to 1 mg/mL. There is a high specificity and positive predictive value comparable to indirect challenges
- Specificity and positive predictive value near 100%
- Symptoms must be clinically current
- A negative MCT does not rule out seasonal asthma

13 Interpretation of the Results

Summary

- Diagnosis should not be made on “numbers” alone
- Consider: history, symptoms (current and past), reasons for testing, spirometry quality, predicted values used, technologist notes
- Remember that lives are affected by these results!
 - Ability to work in the military
 - Changing careers
 - Insurance, disability, legal claims

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Additional Safety Considerations

- Ensure that all staff performing Provocholine® challenge tests are trained on all equipment and emergency airway procedures
- Physician trained in treatment of acute airflow obstruction should be in hospital or available in case of emergency
- Good ventilation in room of test recommended (at least two complete exchanges of air per hour)
- Never leave patients unattended during testing

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Additional Safety Considerations

- Technologists with asthma should avoid testing or take extra precautions (e.g. masks, filters)
- Technologists should stand away from aerosol
- Technologists who perform a MCT should have a negative methacholine test initially and annually thereafter
- Medications to treat severe bronchospasm must be present in testing area
- Oxygen should be readily available
- Stethoscope, sphygmomanometer and oximeter should also be available

15 Reimbursement

CPT Codes for Pulmonary Function Testing

CPT Code # 94010 Spirometry, including graphic record, total and timed vital capacity, expiratory flow rate measurement(s), with or without maximal voluntary ventilation

CPT Code # 94070 Bronchospasm provocation evaluation, multiple spirometric determinations as in 94010, with administered agents (e.g., antigen(s), cold air, methacholine)

CPT Code # 95070 Inhalation bronchial challenge testing (not including necessary pulmonary function tests); with histamine, methacholine or similar compounds

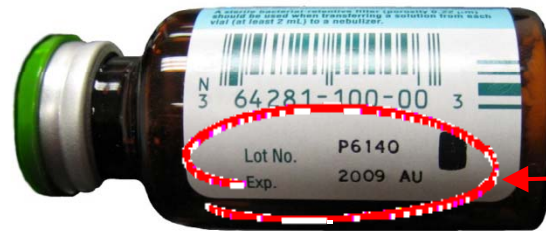
HCPCS # J7674 Methacholine chloride administered as inhalation solution through a nebulizer, per 1 mg; Must be billed with 95070

16 How Supplied / Contact Us

How Provocholine[®] is Supplied



- Supplied in 20 mL amber glass vials containing 100 mg methacholine chloride powder for reconstitution with 0.9% NaCl containing 0.4% phenol (pH 7.0)
- Supplied in boxes of 6 vials
- Prior to dilution, Provocholine[®] powder is stable at room temperature for 3 years – each vial has an expiry date printed on it.



16 How Supplied / Contact Us

Wholesaler Ordering Codes for Provocholine®

Amerisource Bergen

Provocholine®

Pkg. 6 #4294591

Saline with Phenol:

10 x 30 mL #4375382

Morris & Dickson

Provocholine®

Pkg. 6 NDC# 64281-100-06

Saline with Phenol:

10 x 30 mL #414532

Cardinal

Provocholine®

Pkg. 6 # 2991065

Saline with Phenol:

10 x 30 mL #386230-67710

1 x 100 mL #386213-67701

25 x 100 mL #386213-67725

H.D. Smith Wholesale

Provocholine®

Pkg. 6 #1149046

Saline with Phenol:

10 x 30 mL #1149061

McKesson

Provocholine®

Pkg. 6 #199-4359

GIV and Insource, Inc

Provocholine®

Pkg. 6 #1006

16 How Supplied / Contact Us



We welcome your questions. Please contact us as follows:

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Fax: 1.866.265.2174 (toll free from U.S.A.) | 519.751.9149

E-mail: sales@methapharm.com

Web Page: www.methapharm.com

17 Primary References

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18 Additional References

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